HHS Public Access

Author manuscript

Am J Gastroenterol. Author manuscript; available in PMC 2016 July 01.

Published in final edited form as:

Am J Gastroenterol. 2016 January ; 111(1): 12–14. doi:10.1038/ajg.2015.219.

Gluten Introduction, Breastfeeding, and Celiac Disease: Back to the Drawing Board::

Statement Prepared by the Executive Council of the North American Society for the Study of Celiac Disease (NASSCD)

Benjamin Lebwohl, MD, MS and **Joseph A. Murray, MD**

Celiac disease now affects nearly 1% of the population of the United States, [1] and diagnosis rates have continued to increase in recent years.[2] The rise in celiac disease diagnoses does not merely reflect an increased awareness of this immune-based condition on the part of patients and physicians. The seroprevalence of markers for celiac disease among asymptomatic individuals has risen markedly (four-to-fivefold) in recent decades.[3] Although the genetic basis of celiac disease has been well-established, including a necessary set of Human Leukocyte Antigen (HLA) haplotypes and multiple weaker relationships identified by genome wide association studies, the rapidity of this rise points to the role of the environment in triggering the loss of immune tolerance to gluten.

It has long been thought that it may be possible to reduce the likelihood of celiac disease in children by prolonged breastfeeding and altering the introduction of timing of gluten to the diet of infants at risk of celiac disease. An epidemic of celiac disease among young children in Sweden during the 1980's and 1990's was attributed to a number of feeding practices thought to be conducive to the loss of tolerance to gluten, including a lack of breastfeeding and high gluten content during its first introduction.[4] The notion of a “window of tolerance” was supported by a prospective cohort study that found that the risk of celiac disease was greater among infants whose first exposure to gluten occurred prior to age four months or beyond age six months.[5] The mechanism for this “window of tolerance” was thought to be related to the relationship between gluten and the gut barrier; introduction prior to maturation of this barrier (prior to four months), or a large initial gluten load after six months, may induce innate immune activation.[5] But the fact that these inferences were drawn from observational studies, as well as inconsistent findings regarding the protective

Corresponding author: Joseph A. Murray, MD, Division of Gastroenterology and Hepatology, Mayo Clinic, 200 1st St SW, Rochester, MN 55905, Tel: 507-255-5713, Fax: 507-255-6318, murray.joseph@mayo.edu.
On behalf of the NASSCD:
Infant Feeding Workgroup Chair: Elena F. Verdú, MD, PhD
Executive Council: Sheila E. Crowe, MD, Melinda Dennis, RD, Alessio Fasano, MD, Peter H.R. Green, MD, Stefano Guandalini, MD, Chaitan Khosla, PhD

Conflict of Interest/Study Support: Guarantor of the article: Joseph A. Murray, MD

Specific author contributions: Planning and/or conducting study: all authors
Collecting and/or interpreting data: all authors
Drafting the manuscript: B Lebwohl, JA Murray
Final review of the manuscript: All authors

Potential competing interests: None

effect of breastfeeding, [6] left some uncertainty about the optimal approach to prevent celiac disease.

Two recently published randomized trials of infant feeding practices have now brought the strategy of environmental intervention into sharp relief. Their results provide clarity for prospective parents of newborns at risk for celiac disease as well as reassurance for parents who have often wondered if whatever feeding practice they took might have contributed to the risk of celiac disease in their children. These studies were large, multicenter, with long-term follow-up, and the results of their interventions were resoundingly negative.

The first study, conducted at 20 centers throughout Italy, compared a delayed strategy of introduction of gluten at 12 months of age to the standard strategy of six months of age.[7] The 553 children in this trial were all at increased risk for developing celiac disease, as they had a compatible HLA haplotype and a first-degree relative with celiac disease. The cumulative prevalence of celiac disease at age 10 years was 16.8% (see Table). This intervention study showed that, while the later introduction of gluten delayed the onset of celiac disease in early childhood, there was no difference between the two groups by the age of 5 or 10 years, suggesting that age of introduction of gluten had very little impact on the ultimate risk for celiac disease later in childhood. It therefore appears that delaying gluten introduction may delay the onset of celiac disease but does not reduce its incidence.

The second study, a double-blind placebo-controlled trial conducted in eight countries, tested the commonly-recommended practice of introducing small amounts of gluten at four months of age.[8] Infants (n=944) with an at-risk HLA haplotype and a first-degree relative with celiac disease were randomly assigned either 200mg of vital wheat gluten or placebo at that age, and then dietary gluten was introduced to both groups at age six months. It had been thought that this intervention of low-dose gluten exposure at an early age would give the immune system the opportunity to learn to tolerate gluten. At age 5 years the cumulative prevalence of celiac disease was 12.1%, and there was no significant difference in risk of celiac disease when comparing the intervention to the placebo group (Hazard Ratio [HR] 1.23; 95%CI 0.79-1.91).

Moreover, in neither trial was breastfeeding duration found to have any effect on the risk of celiac disease. This finding is in contrast to the protective effect of breastfeeding found in a number of autoimmune diseases, including type 1 diabetes, [9] multiple sclerosis [10] and rheumatoid arthritis. [11] These protective effects have been attributed to the fact that human breastmilk contains numerous immunomodulating as well as antimicrobial molecules. These include immunoglobulins, lactoferrin, alpha-lactalbumin, oligosaccharides and glycoconjugates, lipids, nucleotides, growth factors and cytokines. Breast milk contains leukocytes that can be taken up by the infant and provide immunological protection and transfer of information [12] Breastfeeding also appears to promote a gut microbiome that enhances epithelial barrier. [13] Despite multiple plausible mechanisms, these trials did not find that a protective effect of breastfeeding with the regard to the risk of celiac disease.

Where to next? We must acknowledge that these null results are unequivocal and disappointing. The promise suggested by observational studies, together with our notions

regarding how and why celiac disease develops, have met the stark reality of two well-designed trials that both failed to demonstrate a way to reduce the risk of celiac disease. These results indicate that in this population of children at high risk for celiac disease, the practice of modifying the quantity or delaying the timing of the introduction of gluten to 12 months or introducing gluten between 4 to 6 months likely has little effect.

But disappointment should not lead to nihilism. Rather, this is a “back to the drawing board” moment for the celiac disease community. These results must bring us back to focus on what environmental factors may be operating in these children at risk for celiac disease and how these environmental factors interact with their increased genetic risk to produce celiac disease at such a young age.

It remains indisputable that gluten is the key environmental trigger of celiac disease, and is central to its pathogenesis. But the rise in celiac disease prevalence in recent decades, in the face of stable genes in this relatively short time span, mandates a hunt for other environmental elements that have tilted increasing numbers towards the loss of gluten tolerance. A recent international observational study of children found that residence in Sweden was associated with a doubling of celiac disease risk compared to that of the United States, independent of sex, family history, or HLA type, pointing to some unknown environmental exposure.[14] A host of environmental risk factors for celiac disease have been proposed in recent years based on observational studies. These include prenatal exposures, such as maternal iron use during pregnancy, [15] and infections in children and adults with rotavirus[16] and *Campylobacter jejuni*. [17] The increased risk of celiac disease after exposure to antibiotics[18] or to elective Caesarian section[19] points towards the microbiome as having a modulatory effect on celiac disease risk. It may be the case that individuals at risk for celiac disease develop it in adulthood when an environmental factor such as an infection, medication, or dietary change destabilizes the microbiome. Pending corroboratory evidence relating any or all of these factors to celiac disease pathogenesis, these proposed risk factors may be promising candidates for exploratory prospective studies. [20] It should also be noted that the role of epigenetic factors has not been addressed.

These trials also underscore the importance of HLA haplotype on the risk of developing celiac disease. Indeed, in both studies the main predictor of celiac disease was the HLA haplotype. In those children with the highest genetic risk type for celiac disease, over one quarter of children developed evidence of celiac disease at an early age (see Table). This has practical implications both for the design of future intervention trials (which could be restricted to the most such high-risk patients and appropriately powered) and for everyday clinical practice. It may be warranted to undertake genetic testing of children at high risk for celiac disease early in life and then identify those who need vigilance for the onset of celiac disease, warranting a low threshold for repeated serological testing.

Given the heroic efforts involved in the design and execution of these clinical trials, we should use the collective action of the celiac disease scientific community to derive as much knowledge as possible from these studies, so as to generate hypotheses and direction for future investigations. As such, the data from these intervention trials should be made available in de-identified form to interested investigators.

We should also recognize that while these negative results are frustrating to parents who are looking for ways to reduce the risk of celiac disease in their children, several promising research developments in the treatment of celiac disease have occurred in recent years. The mainstay of treatment remains a strict gluten-free diet, but multiple non-dietary therapies are in various phases of testing. These include pretreatment of gluten prior to ingestion, intraluminal digestion of gluten during meals, enhancement of intestinal tight junctions, inhibition of transglutaminase, and other mechanisms. [21]

While these studies of high-risk children provide some long-awaited answers, they also raise more questions. Do these results apply to the general population of low risk individuals who do not have a family history of celiac disease? Can tolerance to gluten in celiac disease be regained, as has been observed in a proportion of children who develop a transient elevation of transglutaminase antibody levels?[22] Could infant feeding practices affect the chance of regaining tolerance? Why are we seeing far more celiac disease, despite the fact that wheat consumption has decreased over the past century? Does vital gluten that is added to wheat flour have a role? How can celiac disease occur at any age, even in people who have been exposed to gluten for many years? These are crucial questions that need to be answered if we are to turn back the rising tide of the celiac disease epidemic.

Acknowledgments

Financial support: B Lebwohl:The National Center for Advancing Translational Sciences, National Institutes of Health (UL1 TR000040)

C Khosla: The National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health (R01 DK063158)

References

1. Rubio-Tapia A, Ludvigsson JF, Brantner TL, Murray JA, Everhart JE. The prevalence of celiac disease in the United States. Am J Gastroenterol. 2012; 107:1538–44. [PubMed: 22850429]
2. Ludvigsson JF, Rubio-Tapia A, van Dyke CT, et al. Increasing incidence of celiac disease in a north american population. Am J Gastroenterol. 2013; 108:818–24. [PubMed: 23511460]
3. Rubio-Tapia A, Kyle RA, Kaplan EL, et al. Increased prevalence and mortality in undiagnosed celiac disease. Gastroenterology. 2009; 137:88–93. [PubMed: 19362553]
4. Ivarsson A, Persson LA, Nystrom L, et al. Epidemic of coeliac disease in Swedish children. Acta Paediatr. 2000; 89:165–71. [PubMed: 10709885]
5. Norris JM, Barriga K, Hoffenberg EJ, et al. Risk of celiac disease autoimmunity and timing of gluten introduction in the diet of infants at increased risk of disease. JAMA. 2005; 293:2343–51. [PubMed: 15900004]
6. Szajewska H, Chmielewska A, Piescik-Lech M, et al. Systematic review: early infant feeding and the prevention of coeliac disease. Aliment Pharmacol Ther. 2012; 36:607–18. [PubMed: 22905651]
7. Lionetti E, Castellaneta S, Francavilla R, et al. Introduction of gluten, HLA status, and the risk of celiac disease in children. N Engl J Med. 2014; 371:1295–303. [PubMed: 25271602]
8. Vriezinga SL, Auricchio R, Bravi E, et al. Randomized feeding intervention in infants at high risk for celiac disease. N Engl J Med. 2014; 371:1304–15. [PubMed: 25271603]
9. Virtanen SM, Rasanen L, Aro A, et al. Infant feeding in Finnish children less than 7 yr of age with newly diagnosed IDDM. Childhood Diabetes in Finland Study Group. Diabetes care. 1991; 14:415–7. [PubMed: 2060453]
10. Pisacane A, Impagliazzo N, Russo M, et al. Breast feeding and multiple sclerosis. BMJ. 1994; 308:1411–2. [PubMed: 8019251]

11. Brun JG, Nilssen S, Kvale G. Breast feeding, other reproductive factors and rheumatoid arthritis. A prospective study. Br J Rheum. 1995; 34:542–6.
12. Siafakas CG, Anatolitou F, Fusunyan RD, Walker WA, Sanderson IR. Vascular endothelial growth factor (VEGF) is present in human breast milk and its receptor is present on intestinal epithelial cells. Pediatr Res. 1999; 45:652–7. [PubMed: 10231859]
13. Rogier EW, Frantz AL, Bruno ME, et al. Secretory antibodies in breast milk promote long-term intestinal homeostasis by regulating the gut microbiota and host gene expression. Proc Natl Acad Sci USA. 2014; 111:3074–9. [PubMed: 24569806]
14. Liu E, Lee HS, Aronsson CA, et al. Risk of pediatric celiac disease according to HLA haplotype and country. N Engl J Med. 2014; 371:42–9. [PubMed: 24988556]
15. Stordal K, Haugen M, Brantsaeter AL, Lundin KE, Stene LC. Association between maternal iron supplementation during pregnancy and risk of celiac disease in children. Clin Gastroenterol Hepatol. 2014; 12:624–31 e1-2. [PubMed: 24112997]
16. Stene LC, Honeyman MC, Hoffenberg EJ, et al. Rotavirus infection frequency and risk of celiac disease autoimmunity in early childhood: a longitudinal study. Am J Gastroenterol. 2006; 101:2333–40. [PubMed: 17032199]
17. Riddle MS, Murray JA, Cash BD, Pimentel M, Porter CK. Pathogen-specific risk of celiac disease following bacterial causes of foodborne illness: a retrospective cohort study. Dig Dis Sci. 2013; 58:3242–5. [PubMed: 23812827]
18. Marild K, Ye W, Lebwohl B, et al. Antibiotic exposure and the development of coeliac disease: a nationwide case--control study. BMC Gastroenterol. 2013; 13:109. [PubMed: 23834758]
19. Marild K, Stephansson O, Montgomery S, Murray JA, Ludvigsson JF. Pregnancy outcome and risk of celiac disease in offspring: a nationwide case-control study. Gastroenterology. 2012; 142:39–45 e3. [PubMed: 21995948]
20. Lebwohl B, Ludvigsson JF, Green PH. The unfolding story of celiac disease risk factors. Clin Gastroenterol Hepatol. 2014; 12:632–5. [PubMed: 24211288]
21. Veeraraghavan G, Leffler DA, Kaswala DH, Mukherjee R. Celiac disease 2015 update: new therapies. Expert Rev Gastroenterol Hepatol. 2015:1–15.
22. Matysiak-Budnik T, Malamut G, de Serre NP, et al. Long-term follow-up of 61 coeliac patients diagnosed in childhood: evolution toward latency is possible on a normal diet. Gut. 2007; 56:1379–86. [PubMed: 17303598]

Table

Design and outcomes of two randomized trials of gluten introduction in infants at risk for celiac disease

Authors	Lionetti, et al[7]	Vriezinga, et al[8]
Setting	Italy	Croatia, Germany, Hungary, Israel, Italy, the Netherlands, Poland, Spain
Number of infants randomized	553	944
Intervention	Introduction of dietary gluten at 12 months	200mg of vital wheat gluten at 4 months
Comparator group	Introduction of dietary gluten at 6 months	Placebo at 4 months Introduction of dietary gluten at 6 months
Blinding	Non-blinded	Double-blinded
Age at study termination	7.9 years (median)	4.9-5.0 years (mean)
Prevalence of celiac disease	16.8% at 10 years	12.1% at 5 years
Prevalence of celiac disease among DQ2 homozygotes	25.8% at 10 years	26.9% at 5 years
Hazard ratio	0.9 (95% CI, 0.6-1.4)	1.23 (95%CI 0.79-1.91)